LSU autopsy findings point to endothelium as target in heart

Anne Ford

October 2020—Autopsies conducted at University Medical Center in New Orleans on 22 patients who died from SARS-CoV-2 infection found not the expected typical inflammation of the heart muscle associated with myocarditis but instead scattered individual myocyte necrosis.

Early reports suggested that the heart was a primary target of the infection. In one study, conducted in January and February in Wuhan, China, nearly 20 percent of 416 patients hospitalized with COVID-19 were found to have cardiac injury (Shi S, et al. *JAMA Cardiol*. 2020;5[7]:802–810).

Those findings, however, have not been borne out in the experience of Richard S. Vander Heide, MD, PhD, MBA, professor of pathology at Louisiana State University School of Medicine and director of autopsy services, University Medical Center New Orleans. There, he says, "a large majority of the COVID-19-related deaths to date have been primarily due to lung damage and the resulting respiratory failure."

Still, examinations of the heart during COVID-19 autopsies at University Medical Center have uncovered striking findings—enough of them to make Dr. Vander Heide predict: "I think as we go forward what we're going to find is that the heart may be a long-term consequence of COVID infection."

Given the myocarditis mentioned in early reports, myocarditis was naturally one of the things that Dr. Vander Heide and his colleagues at University Medical Center looked for when performing autopsies on 22 COVID-19 patients (10 male, 12 female; 86 percent African American; median age 68.5 years).

Specifically, "we were interested to find out whether there was a lymphocytic infiltrate into the heart associated with damage to the heart cells themselves, which is what, classically, people associate with myocarditis," he says. "And we did not find anything like that. We did not find typical myocarditis in any way, shape, or form. I kept looking and looking and looking."

All that looking did pay off, albeit in an unexpected way. With routine H&E staining, the team found what Dr. Vander Heide calls "swelling or increased prominence" of endothelial cells in the capillaries. Additional immunostaining on a subset of the sections for lymphocytes, endothelial cells, and DNA/RNA, however, didn't yield anything striking. Or did it?

"As we saw in the H&E, we did not see significant numbers of lymphocytes in the myocardium," he says. "What we did see is that the lymphocytes present seemed to be centered on the blood vessels, if anything. So that confirmed our impression that myocarditis, as it's typically described, really isn't present, and what we were seeing was something involving the small blood vessels and the endothelium."

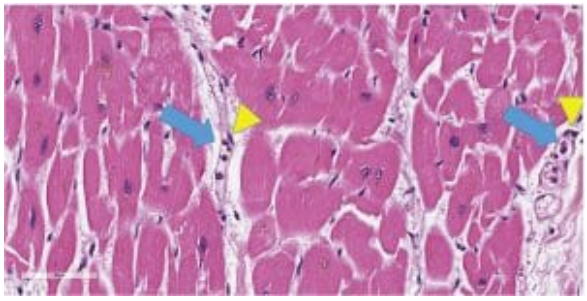
At that point, the team turned to electron microscopy. "In the initial SARS-CoV infection in 2002, there were reports that about 30 percent of patients who had died from SARS had virus identified—or at least viral sequences identified—in the myocytes themselves," he says. "And so we were interested to find out whether there was virus present in the myocytes in SARS-CoV-2." Samples from six COVID-19 autopsies were sent to the University of Delaware's electron microscopy laboratory.

"We did a pretty exhaustive look," Dr. Vander Heide says, and he's glad they did. As he and colleagues wrote in a research letter published July 21 online ahead of print, "Electron microscopy revealed particles consistent with SARS-CoV-2 virus in the myocardial endothelial compartment, pneumocytes, and renal tubular epithelium, but not in the myocytes of six patients examined by EM" (Fox SE, et al. *Circulation.* 2020;142[11]:1123–1125).

"I was very excited," he says. "This confirmed our thinking that maybe it's the endothelium that is the target in the

heart. A lot of data has come out in the last couple of months [showing] that the endothelium is certainly a target for SARS-CoV-2 infection in many different organs. I don't think it's a stretch to think that the heart would certainly be one of the targets, that the virus uses the endothelial cell to gain access to the heart."

Dr. Vander Heide's concerns about potential long-term cardiovascular consequences of COVID-19 appear to be reinforced by a case study that he and his colleagues reported (Fox SE, et al. *Ann Intern Med.* Published online ahead of print July 29, 2020. doi:10.7326/L20-0882). The patient was a 31-year-old female African American who was admitted to University Medical Center for treatment of COVID with typical comorbidities such as obesity, diabetes, and hypertension.



In primary SARS-CoV-2 infection, there is no significant lymphocytic infiltrate. Neutrophils are noted in collections within small vessels (blue arrows) and plump endothelial cells (yellow arrowheads) are common.

"When she was discharged, she didn't have a fever, and her oxygen levels were quite high on room air," he says. "Twelve days later she came back with a sudden fever, neck pain, nausea and vomiting, and sinus tachycardia. They did some workup and found that she had bilaterally enlarged parotid glands—which they thought might be mumps, which is interesting—and some other nonspecific inflammatory responses in the tissue and also in the laboratory values." PCR was negative for SARS-CoV-2. While being evaluated for admission, the patient died after developing hemodynamic instability and ventricular fibrillation.

"We were very interested in that case because that was the first one at the time where we had someone who had had COVID, had recovered, and now had presented later with other kinds of symptoms," Dr. Vander Heide says.

The decedent's family granted permission for an autopsy. While her heart appeared grossly normal, microscopically endotheliitis and vasculitis were present, "diffusely involving the small cardiac vessels and extending into the surrounding epicardial fat and interstitial spaces," Dr. Vander Heide and colleagues wrote in the report.

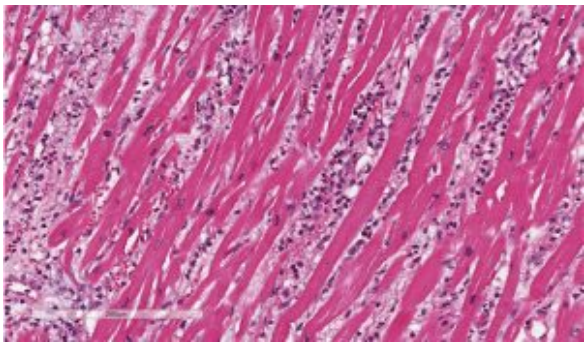
He calls those findings "similar to what we saw with the initial COVID infections, but much worse. There's many more cells involved."

"This might have something to do with the MSIS [multisystem inflammatory syndrome] that people are talking about, which is usually seen in children and young adults, but we think might also be present in this particular young woman of 31," he continues. "What people think at this point with MSIS is that it may be a secondary hyperinflammatory response to the initial SARS-CoV-2 infection. And so we think, with the heart being a more severe vascular response, it fits with that."

Moreover, the case study leads him to speculate that this vascular response is a mimicker of myocarditis in imaging studies. If true, that would explain the recent reports from cardiologists in the clinical literature of something "they think is consistent with myocarditis," he says.

One example: a study conducted in Germany, reported online July 27, that examined 100 patients recently recovered from COVID-19. Of the 78 patients found with cardiac MRI to have some type of cardiac involvement, 60 percent of them "showed some kind of cardiac involvement and what they called 'myocardial inflammation,'" Dr. Vander Heide says (Puntmann VO, et al. *JAMA Cardiol.* 2020. doi:10.1001/jamacardio.2020.3557).

"Some of those studies are very convinced that there's actually myocarditis in these patients," he says. "Because it's centered on the vascular system, and maybe associated with some edema in the heart, which is what they're looking for with their imaging studies, this might be what they're finding—not so much a myocarditis, but this vasculitis, endotheliitis."



In the MSIS-like patient, there is a pattern of brisk endotheliitis/vasculitis involving the small blood vessels and expanding the interstitial spaces.

He hypothesizes further that the alteration of the endothelial structure and function secondary to the SARS-CoV-2 infection of the endothelial space is causing alterations in blood clotting function such that there are small blood vessel clots in the heart that lead to very small amounts of myocyte damage.

"A lot of these patients, if you look at them clinically, have small elevations in troponin T," he says. "The fact that troponin is elevated in these patients to a small degree was always supportive of myocarditis, but it wasn't a large increase in troponin, which always bothered me. And so we think there is small vessel ischemia that's causing these small amounts of myocytes to die and lead to that small elevation in troponin in most of these patients."

Dr. Vander Heide hopes that reports in the literature like those of his team will help call more attention to the role of the heart in COVID-19.

"This stuff that we're starting to describe in the heart is relatively new," he says. "It's interesting, and has been relatively back seat compared to the hypoxia, which is obviously most important for most patients who are in the hospital." He points out that after the 2002–2004 SARS epidemic, "years later, people would show up with heart changes, heart failure, and fibrosis, which indicated there was some damage at some point, but it was not severe enough to cause someone to go to the hospital."

He hopes that in the current pandemic, patients who recover from SARS-CoV-2 infection will be followed, not just those who are very sick and end up on ventilators but also the large number of people who don't become ill enough to be admitted to the hospital. "That population that might get mild or moderate illness and recover—I don't think we know anything about the long-term consequences."

Given how many people have been, are, or will be infected with SARS-CoV-2, that's a sobering thought. As Dr. Vander Heide puts it: "If you've got five or six million people infected, it doesn't take a big percentage of those to cause a sudden, pretty significant increase in long-term cardiac complications. So I think it's important going forward, for clinicians especially, to try to develop lab testing protocols and imaging protocols to follow up some of these patients, because we're going to find out a lot of new information as time goes by."

Anne Ford is a writer in Evanston, Ill.